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Original article

The clinical value of [^{90}Y-DOTA]-D-Phe^{1}-Tyr^{3}-octreotide (^{90}Y-DOTATOC) in the treatment of neuroendocrine tumours: A clinical phase II study

C. Waldherr,[1] M. Pless,[2] H. R. Maecke,[3] A. Haldemann[4] & J. Mueller-Brand[1]

[1]*Department of Nuclear Medicine with PET-Center;* [2]*Department of Oncology;* [3]*Institute of Radiopharmacy, University Hospital, Basel,* [4]*Oncology Institute of Southern Switzerland, Bellinzona, Switzerland*

Summary

Purpose: The aim of this phase II study was to evaluate the tumour response of neuroendocrine tumours to targeted irradiation with the radiolabelled somatostatin analogue ^{90}Y-DOTATOC. In addition, the palliative effect of ^{90}Y-DOTATOC treatment on the malignant carcinoid syndrome and tumour-associated pain was investigated.

Patients and methods: Forty-one patients (mean age 53 years) with neuroendocrine gastroenteropancreatic and bronchial tumours were included. Eighty-two percent of the patients had therapy resistant and progressive disease. The treatment consisted of four intravenous injections of a total of 6000 MBq/m^2 ^{90}Y-DOTATOC, administered at intervals of six weeks.

Results: The overall response rate was 24%. For endocrine pancreatic tumours it was 36%. Complete remissions (CR) were found in 2% (1 of 41), partial remissions (PR) in 22% (9 of 41), minor response in 12% (5 of 41), stable disease (SD) in 49% (20 of 41) and progressive disease (PD) in 15% (6 of 41). The median follow up was 15 months (range 1 month to 36 months). The median duration of response has not been reached at 26 months. The two-year survival time was 76 ± 16%. Eighty-three percent of the patients suffering from the malignant carcinoid syndrome achieved a significant reduction of symptoms. The treatment was well tolerated. A reduction of pain score was observed in all patients (5 of 41) with morphine dependent tumour-associated pain. Side effects included grade III (NCIGC) pancytopenia in 5%, and vomiting shortly after injection in 23%. No grade III–IV renal toxicity was observed.

Conclusion: Targeted radiotherapy with ^{90}Y-DOTATOC is a novel, well-tolerated treatment for neuroendocrine tumours with a remarkable objective response rate, survival time, and symptomatic response.

Key words: endocrine pancreatic tumour, neuroendocrine tumour, octreotide, radionuclide therapy, somatostatine analogue

Introduction

Neuroendocrine tumours (NET), previously known as APUDomas (amine precursor uptake and decarboxylation adenomas) or sporadic islet-cell tumours, are today considered to be malignancies derived from the diffuse neuroendocrine system and share cytochemical features with melanomas, phaeochromocytomas, medullary thyroid carcinoma, and endocrine pancreatic tumours (EPT) [1]. Malignant neuroendocrine tumours and syndromes have a poor prognosis [1]. Surgery is effective in less than 5% of all patients [2, 3]. Management of these tumours includes decreasing the hormone overproduction. This is considered very important because mortality in neuroendocrine tumours is often due to the effects of peptide hypersecretion, rather than tumour progression [1, 4]. More than 90% of islet-cell tumours express somatostatin receptors [1]. Endogenous somatostatin (SRIF: somatotropin release inhibiting factor) acts as an inhibitor of numerous endocrine and gastrointestinal functions, notably reducing plasma concentrations of many peptides including insulin, glucagon, gastrin, secretin, cholecystokinin, and motilin, released by islet-cell tumours. In addition it inhibits the action of these hormones. The development of the metabolically stable somatostatin analogue octreotide, which contains the biologically active part of somatostatin, resulted in a new approach to the treatment of neuroendocrine tumours and the carcinoid syndrome [1, 4–7]. In recent years the aim of many research groups in Nuclear Medicine and Radiopharmacy has been to develop a somatostatin analogue which has a high affinity to the somatostatin receptor and could be linked to a therapeutic β-emitting radioisotope. β-Particles emitted from a radiolabelled peptide bound to a tumour cell also kill neighboring cells, because the path length of β-particles can extend over several cell diameters. The crossfire of β-particles can in theory destroy both somatostatin receptor- positive and -negative tumour cells. In 1996 Maecke et al. constructed the first promising DOTA (tetraazacyclo-dodecanetetra-acetic acid) chelated somatostatin analogue [8], a hydrophilic peptide vector, which can be labelled stably with either the β-emitting therapeutic radionuclide ^{90}Y or diagnostic ^{111}In [9–15]. The affinity of DOTATOC ([^{90}Y-DOTA]-D-Phe^{1}-Tyr^{3}-octreotide) for somatostatin receptor subtypes SSTR 2

and SSTR 5, tested *in vitro*, was found to be very high [9–15]. In the phase I study we could demonstrate a high response rate in patients with neuroendocrine tumours of gastroenteropancreatic or bronchial origin. In this study the maximum tolerated dose was 6000 MBq/m^2. Thirty-three percent of the patients in a phase I study who received cumulative doses of > 8500 MBq/m^2 ^{90}Y-DOTATOC showed dose limiting renal toxicity (DLT) [12]. The present study is a prospective phase II trial investigating the tumour response of neuroendocrine tumours and the palliative effect of ^{90}Y-DOTATOC treatment on the malignant carcinoid syndrome.

Patients and methods

Selection of patients

Inclusion criteria included: 1) histologically confirmed diagnosis of neuroendocrine tumours; 2) tumours had to have an higher uptake in ^{111}In-DOTATOC- or Octreoscan®-scintiscans than the physiological liver or renal uptake; 3) no concurrent antitumour treatment; 4) life expectancy longer than six months; 5) adequate organ function (WHO grade ⩽ 2); 6) written informed consent.

Exclusion criteria: Patients younger than 18 years, pregnancy, history of life-threatening atopic reactions or severe concomitant illness including severe psychiatric disorders.

The study was approved by the local ethical committee and the Swiss authorities.

Radiotracer

Maecke et al. developed a DOTA modified somatostatin analogue named DOTATOC (DOTATOC: 1,4,7,10-tetra-azacyclododecan-4,7,10-tricarboxy-methyl-1-yl-acetyl-D-Phe^1-Tyr^3-Octreo-tide) in a five step synthetic procedure performed according to GMP practice [8–12]. ^{111}In-DOTATOC was prepared according to previously described procedures using 8 µg of DOTATOC dissolved in 190 µl 0.4 M sodium acetate buffer (pH 5.5) with 7 mg gentisic acid and 6 mCi $^{111}InCl_3$ (0.05 M HCL, Mallinckrodt Med., Petten, The Netherlands). The solution was heated at 95 °C for 25 min and quality controlled by using Sep-Pak®C18 cartridge and high performance liquid chromatography (HPLC). As a therapeutic radiometal the pure β-emitter ^{90}Yttrium was linked stably to DOTATOC with preservation of receptor binding affinity (K_D = 2.6 ± 0.5 nM and a labelling yield of > 99.5%).

Treatment

A fractionated treatment protocol was performed with four escalating intravenous injections (925 MBq/m^2, 1295 MBq/m^2, 1665 MBq/m^2, 2035 MBq/m^2) administered at six week intervals resulting in a total of 6000 MBq/m^2 ^{90}Y-DOTATOC. For each session, patients were hospitalized for 2–3 days in accordance with the requirements for legal radioactivity protection and scintigraphic localization control Thirty minutes before the injection of each treatment dose, 500 ml of Hartmann–Hepa 8%-aminoacid solution (Ringer Lactate Hartmann, Proteinsteril® Hepa 8%, Mg 5-Sulfat®) were administered to inhibit the tubular reabsorption of the radiopeptide DOTATOC. In each ^{90}Y-DOTATOC session, 3 mCi of ^{111}In-DOTATOC were injected simultaneously in order to check DOTATOC binding and tumour response. One, twenty-four and forty-eight hours p.i. static images (5 min/image) were acquired by using a large field of view gamma camera (Siemens Diacam), equipped with a medium energy parallel hole collimator (matrix 64 × 64, zoom 1).

Evaluation of response and toxicity

Four weeks before the first and 2–3 months after the last internal radiotherapy, tumour response was monitored by either conventional computed tomography (CT), ultra-sonography (US), magnetic resonance imaging (MRI) or ^{18}F-fluoro-deoxyglucose positron emission tomography (FDG-PET). FDG-PET served only to determine progressive disease.

Tumour response was defined according to the WHO standard criteria. A complete reevaluation of tumour response and time to progression, including radiographic scans, blood counts and chemistries, was performed by the responsible general practitioners or the cancer centers caring for the patients every three months after therapy. Complete blood cell and platelet counts were obtained weekly for at least six weeks after therapy and every three months thereafter. In addition thyroid-stimulating hormone (TSH) was measured every treatment cycle and every three months thereafter. Side effects of ^{90}Y-DOTATOC treatment were investigated and scored according to the National Cancer Institute Grading Criteria (NCI-CTC).

Survival

The overall survival of 24 months for all patients was calculated by the Kaplan–Meier method.

Malignant carcinoid syndrome and tumour associated pain

General practitioners or Cancer Centers were requested to complete detailed reports concerning the patients symptoms and their analgetic treatment.

Results

Patients

Forty-one patients entered the study. The characteristics are given in Table 1. The median age of the patients (male n = 25, female n = 16) was 50.6 years, range 19–76 years. Tumour histologies were as follows: endocrine pancreatic tumours (three insulinomas and one gastrinoma) in fourteen patients, intestinal neuroendocrine tumours in eight patients, bronchial neuroendocrine tumours in seven patients, neuroendocrine tumours of unknown origin in eight patients and finally one paraganglioma, one carotid body tumour, one phaeochromocytoma and one primitive neuroectodermal tumour. Eighty-three percent of the patients (34 of 41) showed a progressive disease before treatment (Table 2). Seventeen percent (7 of 41) had a stable disease before entering the study; none of these patients had any antitumour therapy at least two years before ^{90}Y-DOTATOC-treatment. The details of pre-treatment are shown in Table 1. Thirty-nine patients received four cycles of treatment within twenty-four weeks; in two patients treatment had to be stopped after the second cycle due to tumour progression.

Evaluation of tumour response

The tumour response of the individual tumour types are demonstrated in Table 2.

Table 1. Patients and previous treatments.

	Resection	Chemo-embolisation	Chemo-therapy	Octreotide	Interferon-α	External radiotherapy	Liver-trans-plantation
EPT (n = 14)	8	–	6	–	–	1	1
Intestinal NET (n = 8)	7	–	4	2	2	1	–
Bronchial NET (n = 7)	7	1	–	1	1	1	–
NET of unknown origin (n = 8)	3	1	3	1	–	3	2
Others (n = 4)	2	1	2	1	–	1	–
All (n = 41)	27	3	15	5	3	7	3

Table 2. Tumour response (WHO standard criteria).

	Progression before treatment % (n)	Complete remissions (CR) n	Partial remissions (PR) n	Stable disease (SD) n	Progressive disease within or after treatment	Overall tumour response %	CR, PR, SD n (%)
EPT (n = 14)	71 (10)	–	5	7	2	36	12 (86)
Intestinal NET (n = 8)	88 (7)		1	6	1	13	7 (88)
Bronchial NET (n = 7)	100 (7)	1	1	5	–	29	7 (100)
NET of unknown origin (n = 8)	50 (4)	–	2	5	1	25	7 (89)
Others (n = 4)	100 (4)	–	–	2	2	0	2 (50)
All (n = 41)	83 (34)	1	9	25	6	24	35 (85)

Tumour response was monitored by conventional computed tomography (CT) in 24 cases, ultrasonography in nine cases and magnetic resonance imaging (MRI) in seven cases. In one patient the result of FDG-PET served to determine progressive disease by counting the rate of hypermetabolic lesions. In addition scintigraphic assessments were performed in all 41 patients. Even though there are no defined response criteria for scintigraphy, the findings were concordant with the radiological response in all cases.

Complete remissions were found in 1 of 41 (2%), partial remissions in 9 of 41 (22%) and stable disease in 25 of 41 (61%). The overall tumour response rate was 24%. For patients with EPT, the response rate was 36%. CR or PR were found in liver metastases, diameter 1–7 cm, in eight patients; in lymph nodes (paratracheal, retroperitoneal and mediastinal), diameter 1,5–2 cm, in three patients; in pancreatic primaries, diameter 5–7 cm in two patients. CR could be determined in liver metastases with a diameter <4 cm in two patients and in lymph nodes with a diameter <2 cm in two patients. The median duration of response has not been reached at 26 months. Six of nine patients (67%) have shown continuous remission to date. All responding patients had progressive disease prior to ^{90}Y-DOTATOC-treatment. In four patients ^{90}Y-DOTATOC was able to eliminate all liver metastases, as determined by CT-scan. One patient who had been bedridden because of neuroendocrine spinal metastases achieved a marked improvement in neurological function.

Survival

After a median follow-up of 15 months (range 2 to 26 months) 8 of 41 (20%) patients had died after therapy. Tumour-related reasons for death were: tumour progression in five patients, and a gastrointestinal bleeding in one patient caused by tumour infiltration, as determined by autopsy. Also confirmed by autopsy findings, tumour-unrelated reasons for death were a lethal complication after cardiac surgery six months after treatment in one patient, and acute pneumonia in one patient. No death could be related to the ^{90}Y-DOTATOC-treatment. Figure 1 shows the two-year survival of our study group. The overall survival at 24 months including the 95% confidence interval was calculated to be 76% (60%–92%).

Toxicity

Eleven patients (27%) developed nausea, vomiting and flush during the ^{90}Y-DOTATOC injection. Three patients showed nausea grade 1 after each cycle and three patients exhibited nausea grade 1 for two weeks.

Twenty-two percent (n = 9) of the patients showed lymphocytopenia grade 1, 7% (n = 3) grade 2 and 5% (n = 2) grade 3. After 3-4 weeks values returned to baseline, and the treatment could be given according to protocol to all patients.

After the third cycle of ^{90}Y-DOTATOC-treatment, two patients developed both anamia grade 3 and thrombocytopenia grade 3. Both patients started the treatment with anaemia and thrombocytopenia grade 2. Complete

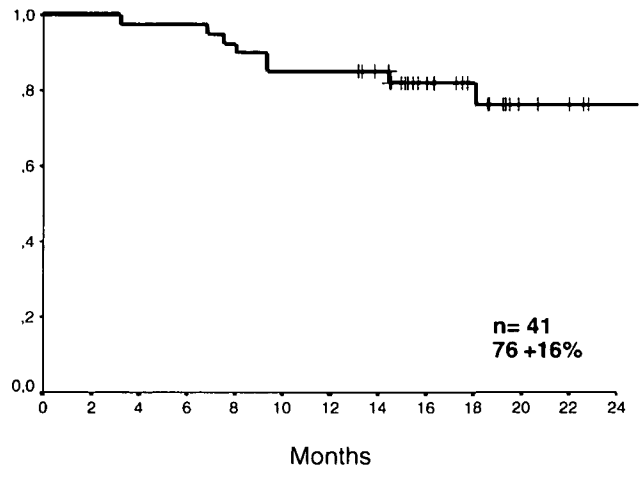

Figure 1. A plot of overall actuarial survival of all 41 patients calculated by the Kaplan–Meier method

TSH-measurement data of 4 values in 21 patients and incomplete data of 2–3 measurements in 20 patients showed normal values throughout the whole trial.

During the trial and the follow up no renal toxicity was observed.

Malignant carcinoid syndrome

Six of forty-one patients suffered from the Malignant Carcinoid syndrome in spite of taking octreotide before ^{90}Y-DOTATOC-therapy. Six of them suffered from diarrhea grade 2, 6 from flushes, 5 from vomiting and 2 from pellagra. After treatment, symptoms were significantly improved in four of six patients (by more than 1 grade on the NCI-CTC score) or completely disappeared in two of six patients.

Tumour-associated pain and weakness

Twenty-two of forty-one patients suffered from pain mainly caused by bone or liver metastases. Five of them had morphine-dependent pain. After ^{90}Y-DOTATOC-treatment all of these patients were able to change to non-steroidal anti-inflammatory drugs (NSAID, three of five) or to discontinue analgetic drugs altogether (two of five). All of these patients had taken increasing doses of NSAID before starting morphine medication. The improvement of pain was not correlated to tumour response.

Discussion

For metastasized NET, biotherapy with the somatostatin analogues octreotide or lanreotide is the treatment of choice [4, 16]. Somatostatin therapy with long-acting somatostatin analogues is reported to cause a tumour response in 12% of patients with EPT and a stabilization of disease in 25%–30% of patients [17]. Oeberg found biochemical responses to a long-acting formulation in 40% to 70%, but objective tumour response (WHO) only in 4%–10% [4]. In one further study, in which carcinoids were treated with lanreotide, Rusznniewski et al. showed subjective response rates of 50%, biochemical response rates of 42% but no objective tumour response [17]. Alternatively, interferon-alpha is reported to have a biochemical response rate of 43% in patients with EPT and an objective response rate of 11% [4, 17, 18]. In the case of tumour progression or escalating malignant carcinoid syndrome under the above-mentioned therapies, dose escalation of somatostatin analogues can be tried or alternatively a combination of interferon-alpha with a somatostatin analogue [1, 4, 17, 18]. If these treatments fail patients are usually treated with chemotherapy (streptozotocin and 5-fluorouracil or cisplatinum and etoposide) [4, 16]. Randomized trials have not established a standard chemotherapy and most regimens have response rates of less than 20% [4]. Furthermore patients treated with polychemotherapy usually have to deal with considerable side effects [16, 18–20].

Treatment with ^{90}Y-DOTATOC resulted in an objective response of 24% and even 36% for patients with EPT. Most of the patients were pretreated and had progressive disease. Tumour stabilization could be achieved in 85% of the patients. The two-year overall survival of 76 ± 16% compares favorably to the reports in the literature for patients with advanced and treatment-resistant tumours [21–23]. ^{90}Y-DOTATOC treatment was well tolerated and toxicity was generally mild. Lastly we could show a significant effect of ^{90}Y-DOTATOC in palliation both concerning the malignant carcinoid syndrome and tumour-associated pain. This benefit seemed to be independent of an objective response. The level of pain was not scored in a prospective standard manner and may therefore be biased. However our more recent unpublished results from ongoing studies confirm this observation. The benefit could be in part related to the reduction of hormone oversecretion and a postradiation neurotrauma.

The previously reported renal toxicity was not found in this trial [12]. Although serum creatinine levels represent a relatively insensitive marker of global renal function, and although a median follow up of 15 months is a short time, cumulative doses < 7400 MBq/m^2 seem to be tolerated well by the kidneys [12]. Even though the pituitary gland expresses low levels of somatostatin receptors, it was of importance to evaluate the possible toxic effects of ^{90}Y-DOTATOC on the function of this organ. We could not detect any adverse effect on the pituitary gland by ^{90}Y-DOTATOC.

Our study suggests that ^{90}Y-DOTATOC is probably a very effective therapeutic alternative to the chemo- and biotherapies known to date. Experimental studies have shown the correlation between the amount of radioactivity applied and the tumour response obtained. Today the radioactive dose of ^{90}Y-DOTATOC-treatment is limited by its renal toxicity, because elevated doses raise the risk of renal damage. But if renal peptide reabsorption could be reduced significantly, ^{90}Y-DOTATOC-

treatment could possibly become a first line therapy for metastasized neuroendocrine tumours. One way to improve the present results could be the combination of ^{90}Y-DOTATOC with other forms of therapies for neuroendocrine tumours.

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References

1. Jensen RT, Norton JA. Carcinoid tumors and the carcinoid syndrome. In DeVita VT, Hellman S, Rosenberg SA (eds): Cancer: Principles & Practice of Oncology, 5th edition. New York: Lippincott-Raven 1997; 1706.
2. Higgins GA, Recant L, Fischman AB. The glucagonoma: Surgically curable diabetes. Am J Surg 1979, 137. 142–8.
3. Prinz RA, Dorsch TR, Lawrence AM. Clinical aspects of glucagon producing islet cell tumors Am J Gastroenterol 1981; 76: 125–31.
4. Oeberg K. Advances in chemotherapy and biotherapy of endocrine tumors. Curr Opin Oncol 1998; 10· 58–65.
5. Kvols LK, Moertel CG, O'Connell MJ et al. Treatment of the malignant carcinoid syndrome: Evaluation of a long-acting somatostatin analogue. N Engl J Med 1986: 315. 663–6.
6. Krenning EP, Bakker WH, Breeman WA et al. Localization of endocrine related tumors with radioiodonated analogue somatostatin. Lancet 1989, 1. 242–4.
7. Lamberts SW, Bakker WH, Reubi JC, Krenning EP. Somatostatin receptor imaging in the localization of neuroendocrine tumors. N Engl J Med 1990; 323· 1246–9.
8. Béhé M, Heppeler A, Maecke HR. New somatostatin analogs for SPET and PET. Eur J Nucl Med 1996; 23: 1144 (Abstr).
9. Maecke HR, Béhé M, Froidevaux S et al. DOTA-D-Phe(1)-Tyr(3)-octreotide (DOTATOC): A unique somatostatin receptor ligand for labeling with a variety of metallic radionuclides J Nucl Med 1997; 38: 18P.
10. Heppeler A, Froidevaux S, Maecke HR et al. Radiometal labeled macrocyclic chelator derivatised somatostatin analogue with superb tumor targeting properties and potential for receptor mediated internal radiotherapy. Chem Eur J 1999, 5 1974–81.
11. Otte A, Jermann E, Béhé M et al. DOTATOC: A powerful new tool for receptor mediated radionuclide therapy. Eur J Nucl Med 1997; 24: 792–6
12. Otte A, Herrmann R, Heppeler A et al Yttrium-90 DOTATOC. First clinical results. Eur J Nucl Med 1999; 26: 1439–47.
13. Stolz B, Weckbecker G, Smith-Jones P et al. The somatostatin receptor-targeted radiotherapeutic [90Y]-DOTA-D-Phe1-Tyr3-octeotide ([90Y]-SMT487) eradicates experimental rat pancreatic CA 20948 tumors. Eur J Nucl Med 1998; 25: 668–74.
14. de Jong M, Bakker WH, Krenning EP et al. Yttrium-90 and indium-111 labeling, receptor binding and biodistribution of [90Y]-DOTA-D-Phe1-Tyr3-octreotide, a promising somatostatin analogue for radionuclide therapy. Eur J Nucl Med 1997; 24: 368–71.
15. Cremonesi M, Ferrari M, Zoboli S et al. Biokinetics and dosimetry in patients administered with ^{111}In-Tyr^3-octreotide: Implications for internal radiotherapy with 90Y-DOTATOC. Eur J Nucl Med 1999; 26; 8: 877–86.
16. Faiss S, Scherubl H, Riecken EO. Wiedenmann B. Drug therapy in metastatic neuroendocrine tumors of the gastroenteropancreatic system. Results Cancer Res 1996; 142: 193–207.
17. Ruszniewski P, Ducreux M, Chayvialle JA et al. Treatment of the carcinoid syndrome with long acting somatostatin analogue lanreotide: A prospective study in 39 patients. Gut 1996; 39: 279–83.
18. Sporn JR, Greenberg BR. Empiric chemotherapy in patients with carcinoma of unknown primary site. Am J Med 1990; 88 (1): 49–55.
19. Johanson V, Tisell LE, Olbe L et al. Comparison of survival between malignant neuroendocrine tumours of midgut and pancreatic origin. BJC 1999; 80 (8): 1259–61.
20. Moertel CG, Kvols LK, O'Connell MJ, Rubin J. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Cancer 1991; 68· 227.
21 Mitry E, Baudin E, Ducreux M et al. Treatment of poorly differentiated neuroendocrine tumors with etoposide and cisplatin. Br J Cancer 1999; 81 (8): 1351–5
22 Kim YH, Ajani JA, Carrasco CH et al. Selective hepatic arterial chemoembolisation for liver metastases in patients with carcinoid tumor or islet cell carcinoma. Cancer Invest 1999; 17 (7): 474–8.
23. Frank M, Klose KJ, Wied M et al. Combination therapy with octreotide and alpha-interferon. Effect on tumor growth in metastatic endocrine gastroenteropancreatic tumors. Am J Gastroenterol 1999; 94 (5): 1381–7

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Correspondence to·
Dr C. Waldherr
University Hospital Basel
Department of Clinical Nuclear Medicine
School of Medicine
Petersgraben 4
4031 Basel
Switzerland
E-mail: cwaldherr@uhbs.ch